

Spontaneous Epileptic Recordings from hiPSC-Derived Cortical Neurons Cultured with a Human Epileptic Brain Biopsy on a Multi Electrode Array

Michel H. Y. Hu ^{1,2,†}, Jean-Philippe Frimat ^{1,2,3,4,*,†}, Kim Rijkers ^{3,5}, Olaf E. M. G. Schijns ^{3,5}, Arn M. J. M. van den Maagdenberg ^{1,2}, Jim T. A. Dings ^{3,5}, Regina Luttge ^{4,†} and Govert Hoogland ^{3,5,†}

¹ Department of Human Genetics, Leiden University Medical Centre, 2333 ZA Leiden, The Netherlands; m.h.y.hu@lumc.nl (M.H.Y.H.); a.m.j.m.van_den_maagdenberg@lumc.nl (A.M.J.M.v.d.M.)

² Department of Neurology, Leiden University Medical Centre, 2333 ZA Leiden, The Netherlands

³ Department of Neurosurgery, School for Mental Health and Neuroscience, Maastricht University Medical Centre, 6229 HX Maastricht, The Netherlands; kim.rijkers@mumc.nl (K.R.); o.schijns@mumc.nl (O.E.M.G.S.); jim.dings@mumc.nl (J.T.A.D.); g.hoogland@maastrichtuniversity.nl (G.H.)

⁴ Neuro-Nanoscale Engineering, Department of Mechanical Engineering/Microsystems and Institute for Complex Molecular systems (ICMS), Eindhoven University of Technology, 5612 AZ Eindhoven, The Netherlands; r.luttge@tue.nl

⁵ Academic Centre for Epileptology (ACE), Maastricht University Medical Centre, 6229 HX Maastricht, The Netherlands

* Correspondence: j.p.m.s.frimat@lumc.nl

† The last 2 authors contributed equally to this work.

Abstract: A growing societal awareness is calling upon scientists to reconsider the use of animals in research, which stimulates the development of translational in vitro models. The physiological and architectural interactions between different cell types within an organ present a challenge to these models, particularly for a complex organ such as the brain. Thus far, in vitro brain models mostly consist of a single cell type and demonstrate little predictive value. Here, we present a co-culture of an epileptic human neocortical biopsy on a layer of human induced pluripotent stem cell (hiPSC)-derived cortical neurons. The activity of the cortical neurons was recorded by a 120-electrode multi-electrode array. Recordings were obtained at 0, 3, and 6 days after assembly and compared to those obtained from cortical neurons without a biopsy. On all three recording days, the hybrid model displayed a firing rate, burst behavior, number of isolated spikes, inter-spike interval, and network bursting pattern that aligns with the characteristics of an epileptic network as reported by others. Thus, this novel model may be a non-animal, translational alternative for testing new therapies up to six days after resection.

Keywords: microelectrode arrays; electrophysiology; neuronal networks; neurological disease; epilepsy; IPS

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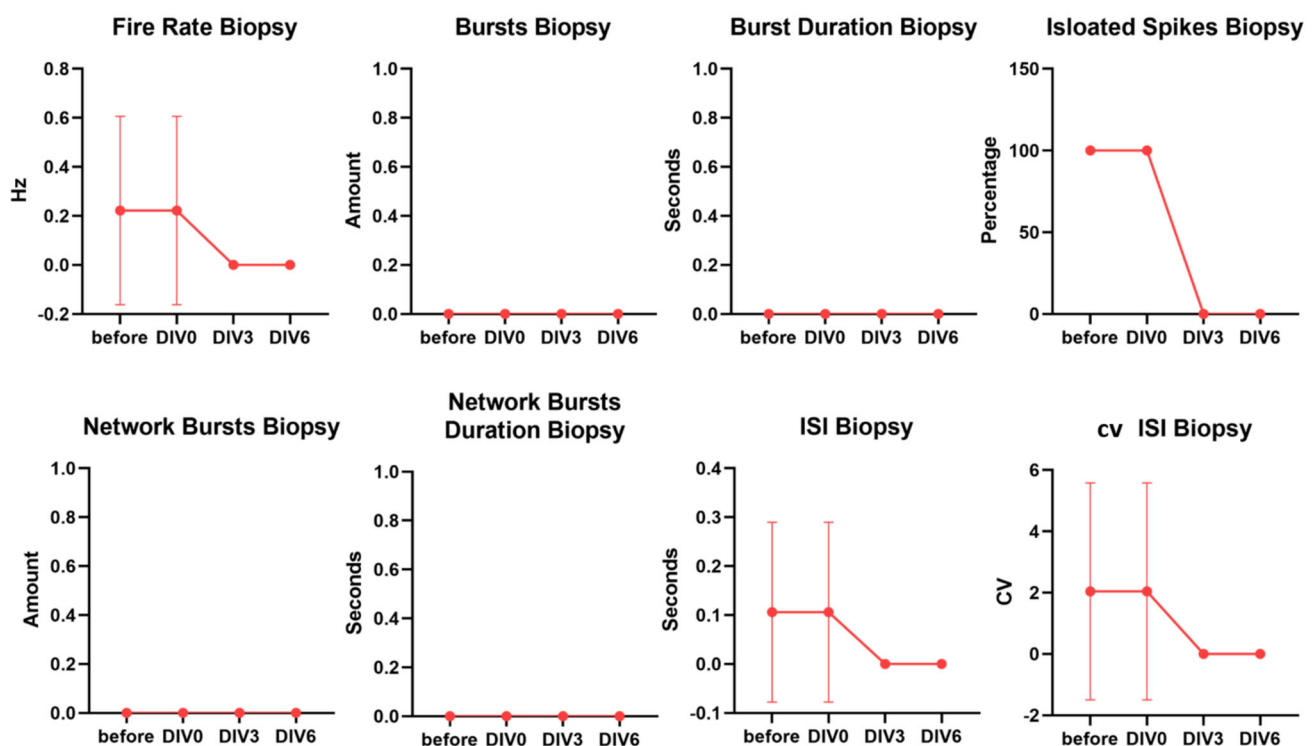
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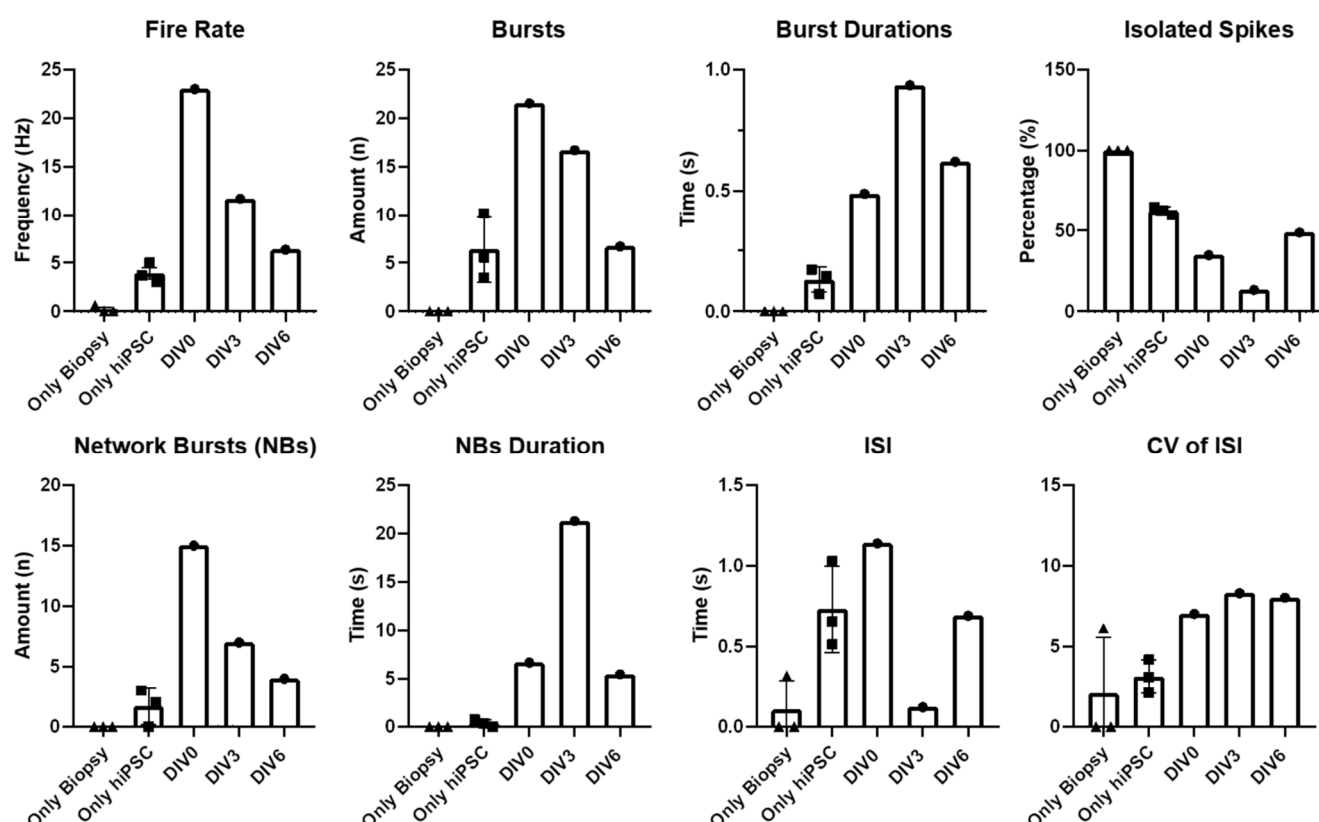
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Parameters	Definitions
Firing rate	Calculated as all spikes that were detected on one electrode divided by the duration of recording. The mean firing rate is calculated by averaging the firing over all the active electrodes.
Burst amount	Calculated as all bursts detected on one electrode.
Burst duration	Total duration of each detected burst averaged over all channels.
Isolated spikes	The number of spikes in all bursts divided by the total amount of spikes in the record.
Network bursts	The number of synchronized network bursts.
Network bursts duration	The cumulative duration of each detected network burst divided by the amount of network bursts.
Inter-spike interval (ISI)	Calculated as the average time between spikes per electrode. The mean ISI of the array is then calculated by averaging the individual electrode ISI averages.
Mean coefficient of variation of ISI	The mean array ISI divided by the standard deviation of the ISIs.

Supplementary Table S1: Selected electrophysiological endpoint parameters and definitions.



Supplementary Figure S1: Electrophysiological characterization (fire rate, burst rate and durations, isolated spikes, network bursts and durations as well as ISI and cv of ISI) of the biopsy alone, showing measurements during the same 6 days periods as the hybrid model. Error bars represent mean with SEM of three 2-minute recordings per condition.



Supplementary Figure S2. Electrophysiological characteristics of the second hybrid model conditions. For each model condition, the firing rate, the burst number and -durations, isolated spikes, the network burst number (NBs) and durations, inter-spike interval (ISI) and coefficient of variation of the inter-spike interval (CV of ISI) is displayed. Model conditions included: 1. The second brain biopsy plug alone (triangles), 2. hiPSC-derived cortical neuron monolayer alone (square), the assembled biopsy plug onto the neuronal cell monolayer (circles) for 3. DIV0 (i.e. day of surgery), 4. DIV3, and 5. DIV6. When the second biopsy plug was assembled on the neuronal cell monolayer, we also recorded an increase in firing rates, bursting and burst durations as well as network burst durations and coefficient of variations of inter-spike intervals, similar to the first biopsy. In addition, we recorded a decrease in isolated spikes but a less pronounced difference in inter-spike interval. Error bars represent mean with SEM of three 2-minute measurements per condition. DIV0, DIV3 and DIV6 are taken from a single 5 minutes recording, which represent a similar recording duration as shown in figure 4 (6 minutes in fig 4).